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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
00014-002002

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on April 5, 2011 (via EFS-WEB)

Signature /Joseph R. Baker, Jr./

Typed or printed name Joseph R. Baker, Jr.

Application Number	Filed
10/045,178	January 11, 2002

First Named Inventor
Noriyuki Kasahara

Art Unit	Examiner
1633	Popa, Illeana

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☑ attorney or agent of record.
Registration number 40900.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Joseph R. Baker, Jr./
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April 5, 2011
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of Noriyuki Kasahara Application No.: 10/045,178 Filed: January 11, 2002 For: A GENE DELIVERY SYSTEM AND METHOD OF USE	)	**MAIL STOP AF** Group Art Unit: 1633 Examiner: Ileana Popa Confirmation No.: 7589

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By: /Joseph R. Baker, Jr./
Joseph R. Baker, Jr.

PRE-APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Pre-appeal Brief is filed in response to the Final Office Action mailed October 5, 2010, in an attempt to promote prosecution and avoid unnecessary burdens on the Patent Office, Examiner and Applicants.

Furthermore, the Applicants would like to point out that the parents of the present application have been examined by two different examiners and resulted in two issued U.S. Patents (6,410,313 and 6,899,871) and that claims of similar scope have been allowed in Europe (see EP 1115290) and Canada (see 2,346,931). More particularly, Applicants wish to point out that the mere passage of 10 years from the priority date of the present application lends itself to improper hindsight reconstruction.

REJECTION UNDER 35 U.S.C. §103

Claims 41, 43-45, 49-51, 56, 61, 66, 70, 71, 75, 78-80, 87, 89, 91, 97-102, 105, 107, 109, 115-119, and 121 stands rejected under 35 U.S.C. §103 as allegedly unpatentable over Ram *et al.* (Cancer Research, 1993, 53:83-88) in view of each of Martuza *et al.* (U.S. Patent No. 5,585,096), Murakami *et al.*, (Gene, 1997, 202:23-29) and Sobol *et al.* (U.S. Patent No. 5,674,486). Applicants traverse this combination and rejection for the reasons that follow. Applicants recognize that additional references are directed to further dependent claims (*e.g.*, Douar *et al.* against claims 119-120; Vile against claims 58, 88, 90, 92, 106, 108 and 110; Kasahara against claims 63-65, 67-69, 73, 81, 82, 93, 95, 103, 104, 111 and 113); however, if an independent claim is non-obvious then any claim depending therefrom is also non-obvious. Accordingly, Applicants have focused this Pre-Appeal Brief on the independent claims and the three references Ram et al, Martuza *et al.* and Murakami *et al.*

The combination of reference provided by the Patent Office requires a large number of variations and assumptions that were beyond the scope of understanding in the art prior to the time of the invention. In other words, the combination arrived at by the Patent Office is the result of hindsight reconstruction utilizing references that one of skill in the art would ***not*** consider relevant to the invention. For example, one of skill in the art would not combine cell transplants (Ram *et al.*), with DNA lytic viruses (Martuza *et al.*), with avian viruses (Murakami *et al.*) to arrive at Applicants' claimed invention.

A *prima facie* case of obviousness requires that the references when combined ***must*** teach or suggest each and every element of Applicants' claimed invention and ***must*** demonstrate a reasonable expectation of success. Applicants' independent claims require, at a minimum, "a replication competent retrovirus that infects mammalian cells . . ." and that comprises an IRES cassette.

I. Combination Does Not Teach Each and Every Element of the Invention

The combination of references, particularly Ram *et al.*, Martuza *et al.* and Murakami *et al.* **fail to teach or suggest each and every element of Applicants' claimed invention**. The table immediately below provides examples of the teachings of the individual references as well as exemplary deficiencies:

Reference	Teaching/suggestion	Does *not* teach or suggest
Ram *et al.*	*Cell* delivery (not viral delivery); defective retroviral DNA in cells wherein the cells are delivered to a subject	Replication competent oncoretroviral nucleic acids; recombinant replication competent oncovirus that infect mammalian cells; delivery of oncovirus to mammals; IRES cassette; location of IRES cassette
Martuza *et al.*	defective DNA lytic virus (NOT a retrovirus)	Replication competent oncoretroviral nucleic acids; recombinant replication competent oncovirus that infect mammalian cells; delivery of oncovirus to mammals; IRES cassette; location of IRES cassette
Murakami *et al.*	Avian Rous Sarcoma Virus; IRES Cassette (replication defective - cannot infect or replicate in mammalian cells).	Replication competent retroviral nucleic acids the propagate in mammalian cells; recombinant replication competent oncovirus that infect mammalian cells; delivery of oncoviruses to mammals

The exemplary table above demonstrates that each of these references fail to teach elements (including the same elements) and thus the teachings are lacking when the references are combined (*i.e.*, the combination fails to teach all the elements of the invention). The combination fails to teach or suggest, for example, recombinant replication competent

oncoretroviral nucleic acids; recombinant replication competent oncoviruses that infect mammalian cells; and delivery of such recombinant replication competent oncovirus to mammals to treat cell proliferative disorders.

First, Ram *et al.* is hardly relevant to Applicants' claimed invention. Ram *et al.* is not directed to viral delivery but rather to delivery of cells. In addition, **Ram *et al.* teach *cells* comprising a defective retroviral genome**. In other words the "vector" of Ram *et al.* is the cell itself comprising portions of a retroviral genome. The Ram *et al.* reference is so far removed from Applicants' invention as to have little bearing or overlapping subject matter; in fact not a single element of Applicants' claimed invention can be found in the Ram *et al.* reference.

In order to overcome the defective cell/virus of Ram *et al.* the Patent Office alleges, "at the time of filing, the advantages of using replication competent retroviruses for cancer treatment was taught by the prior art. For example, Martuza *et al.* . . ." (see, *e.g.*, the Final Office Action at page 3, last paragraph). First, Martuza *et al.* do not teach a retrovirus, rather Martuza *et al.* teach a lytic virus, HSV. Second, **Martuza *et al.* also teach defective viruses** (although not retroviruses). Martuza *et al.* attenuated HSV (*i.e.*, made it defective) in a different way compared to prior art lytic viruses (HSV). Accordingly, the advantages of replication competent retroviruses were not disclosed in Martuza *et al.*

The Patent Office suggests that one of skill in the art would combine HSV vectors of Martuza *et al.* with the defective MLV of Ram *et al.* to obtain replication competent retroviral vectors for gene therapy. This could not be further from the facts. The genomes and life-cycles of HSV and MLV are so different that one of skill in the art would not combine the teachings as suggested by the Patent Office. More importantly, however, is that Martuza *et al.* actually teach a defective or attenuated HSV (see Figure 1 and column 2, lines 40-55 of Martuza *et al.*), thus, what the Patent Office is doing is combining two defective viral systems to allegedly arrive at a replication competent retrovirus. The combination of the references could not result in a replication competent retrovirus as suggested by the Patent Office. The combination of the references teach at most a defective oncolytic retrovirus. Oncolytic retroviruses do not exist, in fact an important aspect of the retrovirus is that it does not lyse the cell.

The Patent Office then proceeds to combine the foregoing references with Murakami *et al.* Again, Murakami *et al.* is directed to yet another species of virus. Murakami *et al.* uses

Rous Sarcoma Virus (RSV). RSV is recognized to have a large gene (*i.e.*, *src*) that can be readily removed and replaced without changing the viral life cycle. In fact, the reason that this viral vector has been used in research is specifically because of the flexibility of the replaceable *src* gene, something not available in MLV. There could be no predictability of using this same structure in MLV because MLV does not have the replaceable *src* gene. In fact, Oh *et al.* (J. of Virol., 76(4):1762-1768, 2002) makes this point very clear at page 1762, column 1, paragraph 2. In that paragraph, the author clearly indicates that most retroviral genomes cannot accommodate the insertion of a significant amount of additional genetic information but for one "***exception***", that exception being RSV. Accordingly, there could be no expectation that inserting an IRES with a heterologous gene into MLV would function (see, also, the Declaration by Dr. Chiang). Furthermore, RSV is incapable of infecting mammalian subjects and thus one of skill in the art would not consider the teachings of Murakami *et al.* as being relevant to treating a mammal. As Jespersen *et al.* (cited by the Examiner) states at page 228, 16 lines from bottom of first column, "However, avian viruses such as RSV and avian leukemia virus are replication defective in mammalian cells." Thus, **Murakami *et al.* also provides vectors that are replication defective in mammals**.

II. No Reasonable Expectation of Success

Furthermore, the combination of references does not teach or suggest any reasonable expectation of success. The Examiner recognizes that defective viruses (Ram *et al.*) do not work effectively. To overcome these deficiencies, the Patent Office combines DNA lytic viruses with avian viruses. DNA lytic viruses are unrelated to retroviruses and thus do not function as retroviruses and RSV does not infect or replicate in mammalian cells (Ram *et al.*, Martuza *et al.* and Murakami *et al.*, respectively). Accordingly, there could be no expectation of success from the combination of the references to arrive at a replication competent retrovirus capable of infecting mammalian cells and having the properties of Applicants' claimed invention.

To address Applicants' position of unexpected properties and lack of predictability or success, the Examiner cites to Jespersen *et al.* (see, page 11, paragraph 8 of Final Office Action) as post filing support for a reasonable expectation of success. However, as previously described in (i) prior responses, (ii) during the in-person interview of 26 March 2009 and (iii) in the Declaration by Dr. Chiang (a disinterested third party expert), the vector

of Jespersen and prior vectors lack the stability and spread of a vector of Applicants' claimed invention. For example, the publication by Paar *et al.* (J. of Virology, pp.6973-6983, July 2007; a publication by a third party) compares the vector stability of Applicants' vector and vectors described by Jespersen *et al.* Paar *et al.* conclude:

> The data obtained clearly demonstrate that insertion of the transgene cassette immediately downstream of the 3' end of the *env* gene generates vectors with better replication kinetics and genomic stability than when an identical transgene cassette is placed in the 5' end of the 3'-LTR U3 region [Jespersen *et al.*] and that Mo-MLV based vectors have better replication kinetics, genomic stability and transgene expression levels than equivalent Akv-MLV-based vectors [Jespersen *et al.*]. (See, page 6981, Discussion).

Accordingly, Paar *et al.* demonstrate Applicants' claimed invention is superior and has unexpected properties that were not recognized by Jespersen *et al.* as alleged by the Patent Office.

As demonstrated to the Examiner and the Examiner's Supervisor during the in-person interview of 26 March 2009, Applicants' claimed invention demonstrates unpredictable results including long term propagation and vector stability as indicated in Paar *et al.* (see above). These cannot be merely dismissed as being unimportant since they provide true benefit to the methods of treatment described by the present disclosure. These features did not exist prior to Applicants' invention.

Thus, the combination of Ram *et al.*, Martuza *et al.* and Murakami *et al.* leads at most to a defective oncolytic virus that infects avian cells. The addition of Sobol *et al.*, Daur *et al.* or Kasahara *et al.* do not remedy the deficiencies of the combination of Ram *et al.*, Martuza *et al.* and Murakami *et al.* Furthermore, there is no reasonable expectation of success or of the unexpected properties as evidence by third party publications and Declarations.

For at least the foregoing reasons, the pending claims are novel and non-obvious over the cited reference. Accordingly, Applicants respectfully request withdrawal of this rejection.

Respectfully submitted,

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Date: April 5, 2011

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